One Institution's Experience With Pancreas Transplantation

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The University of Minnesota has the largest experience with pancreas transplantation of any institution, with 130 cases since 1966, including 116 in 98 patients between July 1978 and June 1985. Currently, 30 patients are insulin-independent, 19 for greater than one year, the longest for seven years. One-year patient and graft survival rates overall are 87% and 30%, respectively. Of 98 recipients, 49 had had previous kidney transplants, while 49 had not, and currently most of the pancreas recipients do not have uremia and have not had a kidney transplant but have early complications of diabetes. A total of 44 of the grafts were procured from related and 72 from cadaver donors. Although 32 of the 116 grafts (28%) failed for technical reasons, the most common cause of graft failure has been rejection. Various immunosuppressive regimens have been used in attempts to reduce the rejection rate, and one combination, low-dose cyclosporine-azathioprine-prednisone (triple therapy), has been particularly effective, with a one-year functional survival rate of 73% in recipients of technically successful grafts from human leukocyte antigen-mismatched cadaver or related donors (N = 20). The pancreas graft survival rates have improved gradually (43% for 1984 to 1985, N = 30; versus 27% for 1978 to 1983, N = 86) for transplants from both related and cadaver donors. Metabolic studies from most recipients with functioning grafts (insulin-independent) show normal or nearly normal results. Preliminary observations on secondary complications suggest a more favorable course in recipients whose grafts have functioned long term than in those whose grafts failed early.

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Between December 16, 1966, and June 6, 1985, 130 pancreas transplants were carried out in two series at the University of Minnesota Medical School.[1] The second series, begun on July 25, 1978, comprises 116 pancreas transplants in 98 patients and has encompassed several changes in surgical technique, graft preservation, recipient immunosuppression and recipient and donor selection in an attempt to evolve an approach that would result in a high success rate. The various techniques, in a rough chronological and overlapping order, include leaving the duct open,[2] duct injection,[3] duct ligation,[4] ductoenterostomy[4] and ductocystostomy. Immunosuppressive regimens have included azathioprine and prednisone,[3] cyclosporine and prednisone[5] and cyclosporine, azathioprine and prednisone in combination.[1,6] Donors have been both cadavers and living relatives.[7-9] Initially, all recipients had previously had kidney transplants, while in recent years most recipients have had neither uremia nor a kidney transplant but have had early or only moderately advanced, but progressive, secondary complications. In this report, we summarize the results of an analysis of pancreas transplant outcome of our second series according to isolated factors and within various subcategories according to combinations of these factors.

Patients and Methods

From July 25, 1978, to June 6, 1985 (Figure 1), 116 pancreas transplants were carried out in 98 patients with diabetes mellitus—49 with previous kidney transplants for end-

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stage diabetic nephropathy, 49 without end-stage diabetic nephropathy—72 from cadaver donors—40 segmental, 32 whole-organ grafts[1,10]—and 44 (all segmental) from related donors—27 human leukocyte antigen (HLA)-identical siblings, of whom 6 were identical twins, 8 HLA-mismatched siblings, 8 parents and 1 cousin. In all, 14 patients received two pancreas transplants, and 4 of these received a third pancreas transplant after the previous grafts failed; all of the retransplants were from cadaver donors. Fifteen of the recipients had previously received kidneys from their related donors—seven HLA-identical siblings, seven mismatched relatives and one identical twin. At the time of primary pancreas transplantation, the patients—38 men, 60 women—ranged in age from 16 to 52 years (mean ± standard deviation of 32.5 ± 6.5 years). The age of onset of diabetes mellitus ranged from 1 to 30 years (mean, 9.9 ± 5.1 years). The duration of diabetes at the time of the pancreas transplant ranged from 10 to 40 years (mean, 22.6 ± 5.7 years). In the recipients who had previously had a kidney transplant, the interval from the kidney to the pancreas transplant ranged from 0.3 to 9.4 years (mean, 3.4 ± 2.3 years).

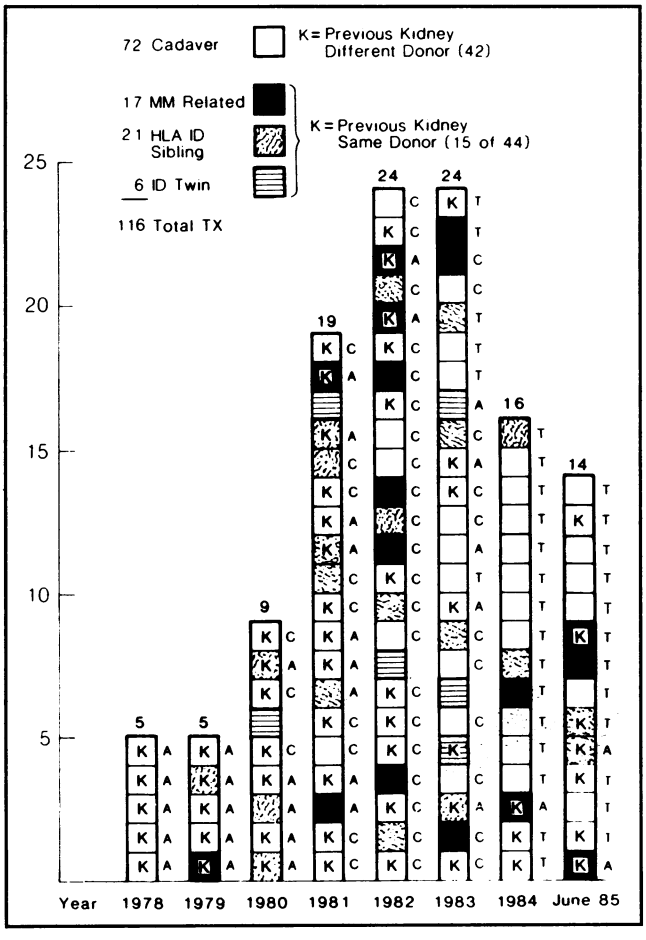

Figure 1.—Number of pancreas transplants by year at the University of Minnesota between July 25, 1978, and June 6, 1985, according to donor source and association with previous kidney transplants. In recipients of previous kidney grafts, the pancreas grafts of living related donors were from the same donor as the kidney with one exception, but those from cadavers were always from a donor different from that for the kidney. The letters to the right of each square indicate the drug regimen: A = azathioprine plus prednisone (N = 34), C = cyclosporine plus prednisone (N = 44), T = cyclosporine plus azathioprine plus prednisone (N = 33). HLA ID = human leukocyte antigen-identical, MM = [HLA] mismatched, TX = transplants

Of the cadaveric grafts, 26 were transplanted immediately after removal from the donor, and 45 were stored for 2 to 26 hours (mean, 11.0 ± 5.5 hours) at 4°C (1 in Collins' solution[2] and 45 in modified silica gel filtered plasma).[11] All but three grafts functioned immediately.[12]

Techniques for management of the exocrine secretion included open-duct intraperitoneal drainage in 15 (10 cadaver, 5 related), duct ligation in 3 (all cadaver), duct injection in 39 (34 cadaver, 5 related), ductoenterostomy in 57 (23 cadaver, 34 related) and ductocystostomy in 2 cases (both cadaver). Of the 32 whole pancreas transplants (all cadaver), 1 was open duct, 15 were duct injected, 14 were anastomosed to a Roux-en-Y limb of recipient jejunum (8 with a large duodenal patch encompassing both the papilla of Vater and the duct of Santorini; 6 of the papilla of Vater only) and 2 were anastomosed to the recipient's bladder. Of graft failures, 32 of the grafts—17 cadaver, 6 HLA-identical siblings (3 who were and 3 who were not previous kidney donors), 7 HLA-mismatched relatives (3 who were and 4 who were not previous kidney donors) and 2 identical twins—failed for technical reasons (1 bladder drained, 3 duct ligated, 3 duct injected, 8 open duct and 17 enteric drained).

Of the 80 recipients of technically successful allografts (55 cadaver, 15 HLA-identical and 10 nonidentical related), 18 (9 cadaver, all with previous kidneys from different donors; 4 HLA-identical siblings with a previous kidney from the same donor; 5 mismatched relatives, 4 with and 1 without previous kidneys from the same donor) were treated with azathioprine and prednisone as the principal immunosuppressants; 39 (28 cadaver, 19 with and 9 without previous kidneys; 8 HLA-identical siblings, and 3 mismatched relatives, none with previous kidneys) were treated with cyclosporine and prednisone as the principal immunosuppressants, and 23 (18 cadaver, 6 with and 12 without previous kidneys; 2 HLA-identical and 2 mismatched relatives without previous kidneys, and 1 HLA identical with a previous kidney from another HLA-identical sibling) were treated with a combination of cyclosporine, azathioprine and prednisone (triple therapy). Rejection episodes were treated with a transient increase in prednisone dose, a temporary course of antilymphocyte globulin or both.

Results

Currently (June 15, 1985), 78 of the 98 recipients are alive, and 30 have functioning grafts and are insulin-independent. Of the 30 patients, 1 has an open-duct graft at 6.9 years; 4 have duct-injected grafts at 2.1, 2.6, 2.8 and 4.5 years; 24 have enteric-drained grafts at less than 1 month (two patients), at 1 month (two patients), at 4 (two), at 5 (three), at 7, at 12 (two), at 13, at 15, at 16, at 18 (two), at 22, at 23 (two), at 28, at 31, at 41 and at 44 months, and 1 has a pancreaticocystostomy at 4 months posttransplant. In all, 27 grafts functioned for at least a year, including 19 of those currently functioning. Two recipients of open-duct grafts and one recipient of an enteric-drained graft began insulin injections for hyperglycemia between two and four years after transplantation, but had C-peptide levels above baseline and they are not prone to have ketosis. Three recipients of duct-injected grafts were insulin-independent for more than a year; one then had

rejection of the graft, while the other two died of cardiovascular disease at more than three years posttransplant, with still-functioning grafts. Two recipients of enteric-drained grafts had rejection of the pancreas transplants at 1.7 and 1.8 years posttransplant.

In the entire series of 116 grafts, losses attributed to technical causes occurred in 32 instances (28%) and to immunologic causes in 48 (41%) cases (44 probable rejection, 4 autoimmune recurrence of disease). Six patients died with functioning grafts.

For all cases, one-year actuarial patient and graft function (insulin-independent) survival rates were 86% and 30%, respectively (Figure 2-A). The survival rate has been significantly higher for recipients of grafts from related than from cadaver donors (95% versus 79% at one year, Figure 2-B). The functional survival rate of related donor grafts has exceeded that of cadaver donor grafts (41% versus 23% at one year) and has been higher for grafts from HLA-identical siblings than from HLA-mismatched relatives (46% versus 34% at one year, Figure 2-C). The benefit of HLA matching was most evident when only technically successful allografts were analyzed; in this subgroup, 76% of grafts from HLA-identical siblings, 58% from mismatched relatives and 30% from cadaver donors were functioning at one year (Figure 2-D).

The transplants from identical twin donors are in a separate category because the first three recipients of technically successful grafts were not immunosuppressed prophylactically and, in all three, hyperglycemia occurred between 6 and 12 weeks. On graft biopsy, this was associated with insulitis without evidence of rejection, thus representing an autoimmune recurrence of the original disease.[13] The process was partially reversed by administering antilymphocyte globulin and azathioprine in the third recipient, while the fourth recipient of an identical-twin pancreas graft was given azathioprine prophylactically beginning at the time of transplantation. The fourth identical twin graft recipient is currently insulin-independent at 1.9 years posttransplant.

Two categories of pancreas donors were associated with particularly high graft function survival rates: HLA-identical siblings and related donors who had previously given a kidney to the recipient, regardless of match. Conversely, the graft function survival rates of HLA-mismatched grafts from either related or cadaver donors in recipients who had not received kidney transplants, or in those who had previously received kidney transplants from a different donor than the pancreas, were low and similar. When all pancreas transplant cases were analyzed, the one-year functional survival rate for allografts from the same living donor as the previous kidney was 60%, while in those who had neither uremia nor a previous kidney transplant who were recipients of grafts from HLA-identical siblings it was 52%. Likewise, the one-year functional survival rate was 22% in recipients of HLA-mismatched grafts (cadaver and related) who had not had kidney transplants and 23% in recipients of cadaver pancreas grafts who had previously received a kidney from a different donor (Figure 3-A). The same analysis done for technically successful allografts alone showed that the one-year functional survival rate for grafts from the same living donor as the previous kidney (four HLA-identical siblings and four nonidentical related, all treated with azathioprine and prednisone) was 100%, and of grafts from HLA-identical siblings in nonuremic, nonkidney transplant patients (ten treated with cyclosporine and prednisone and two with triple therapy) it was 68%; for those who had neither uremia nor a kidney transplant and who received grafts from HLA-mismatched donors (21 cadaver and 6 related; 1 treated with azathioprine-prednisone, 12 with cyclosporine-prednisone, 14 with triple therapy) it was 33%, and for those with a previous kidney transplant who received cadaver pancreas grafts (9 treated with azathioprine-prednisone, 19 with cyclosporine-prednisone, 6 with triple therapy) it was 29% (Figure 3-B). Because until recently the rejection rate was low only in recipients of grafts from HLA-identical siblings or from previous related kidney donors, the influence of duct management techniques could be assessed only in this group of patients, and the highest functional survival rate has been obtained in grafts drained enterically (Figure 3-C).

In 1983 it became apparent that recipient immunosuppressive regimens of azathioprine and prednisone or cyclosporine and prednisone were associated with low functional survival rates for grafts from HLA-mismatched related or cadaver donors, and we began using cyclosporine, azathioprine and prednisone in combination (triple therapy). This change has been associated with improved results, and the one-year actuarial functional survival rate of technically successful grafts from HLA-mismatched donors is 73% in 20 recipients—6 with and 14 without previous cadaver kidneys; 18 cadaver and 2 mismatched related pancreas donors—treated with triple therapy, as compared with one-year graft survival rates of 20% in 10 azathioprine-prednisone and 13% in 31 cyclosporine-prednisone treated recipients of HLA-mismatched grafts (excluding those from a previous kidney donor) from our earlier experience (Figure 3-D).

In all, 32 recipients of technically successful grafts, 12 from related and 20 from cadaver donors, have been treated for rejection episodes as manifested by the occurrence of hyperglycemia several weeks or months after transplantation. Eleven recipients—six with related and five with cadaver donor grafts—reverted to euglycemia and are currently insulin-independent—a 34% response rate overall, 50% in the related-donor and 25% in the cadaver-donor category.

The changes we have made in surgical technique and in immunosuppressive protocols have been associated with a higher success rate of pancreas transplantation (Figure 4-A and B). For all cases, including technical failures, the one-year graft survival rate for transplants done between 1978 and 1983 was 27% (37% for related and 20% for cadaver donor pancreases), whereas for 1984 to 1985 it was 43% (67% for related and 31% for cadaver donor pancreases). Patient survival rates have been similar in both eras (Figure 4-C and D), 85% at one year for primary transplants done between 1978 and 1983—94% for recipients of related and 78% for recipients of cadaver donor grafts—and 88% for primary transplants done during 1984 and 1985—100% for recipients of related and 82% for recipients of cadaver donor grafts. Overall, patient survival rates have been similar in pancreas transplant recipients who have or have not had previous kidney transplants (Figure 5-A), but in each of these categories the patient survival rates were higher in recipients of related than of cadaver donor grafts (Figure 5-B and C).

Metabolic studies in the recipients with functioning grafts have shown that most are restored to a euglycemic state with

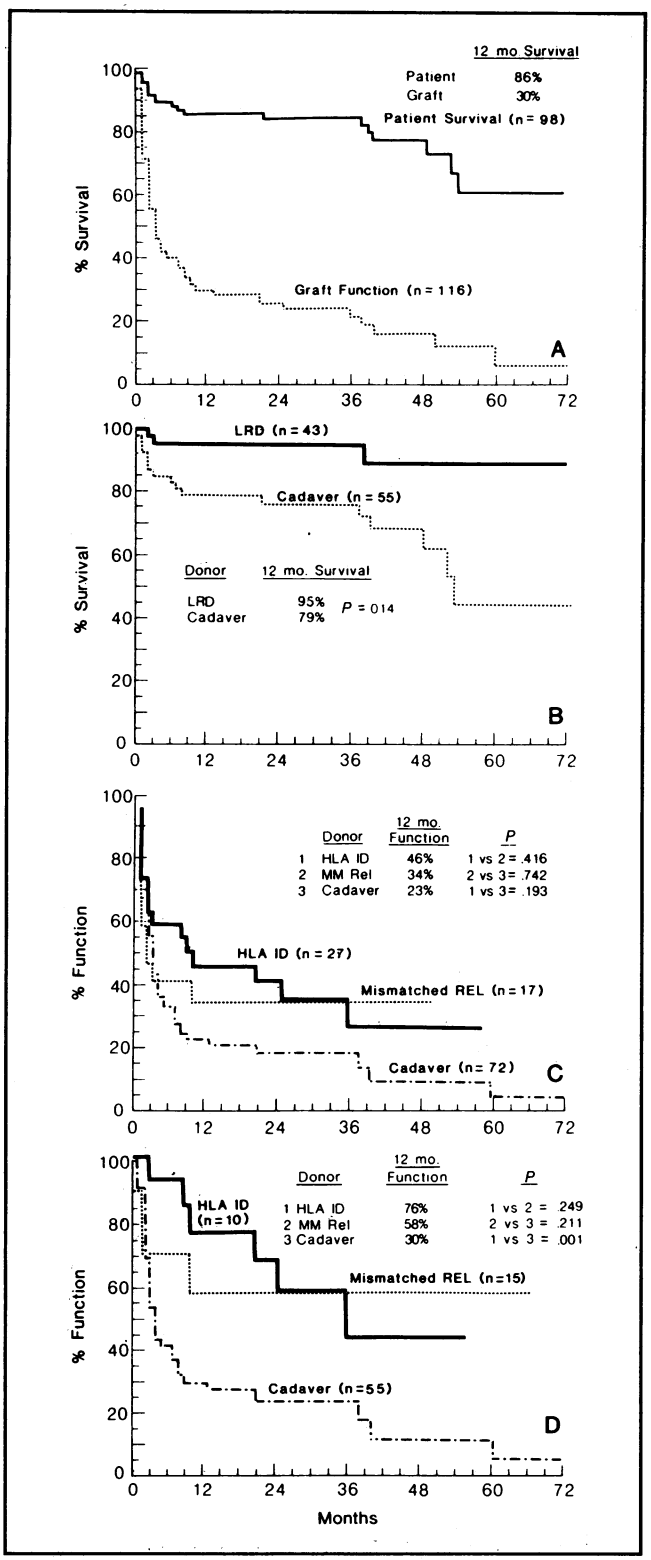

Figure 2.—A, Actuarial patient and graft functional survival rates as of June 15, 1985, for all pancreas transplant cases done at the University of Minnesota between July 25, 1978, and June 6, 1985. **B,** Patient survival rate for all recipients of primary grafts according to whether the donor was a living relative (LRD) or a cadaver. **C,** Pancreas graft functional survival rate according to donor source for all cases, including technical failures. **D,** Functional survival rate, according to donor source, of technically successful allografts only. HLA ID = human leukocyte antigen-identical, MM Rel = [HLA]-mismatched relative

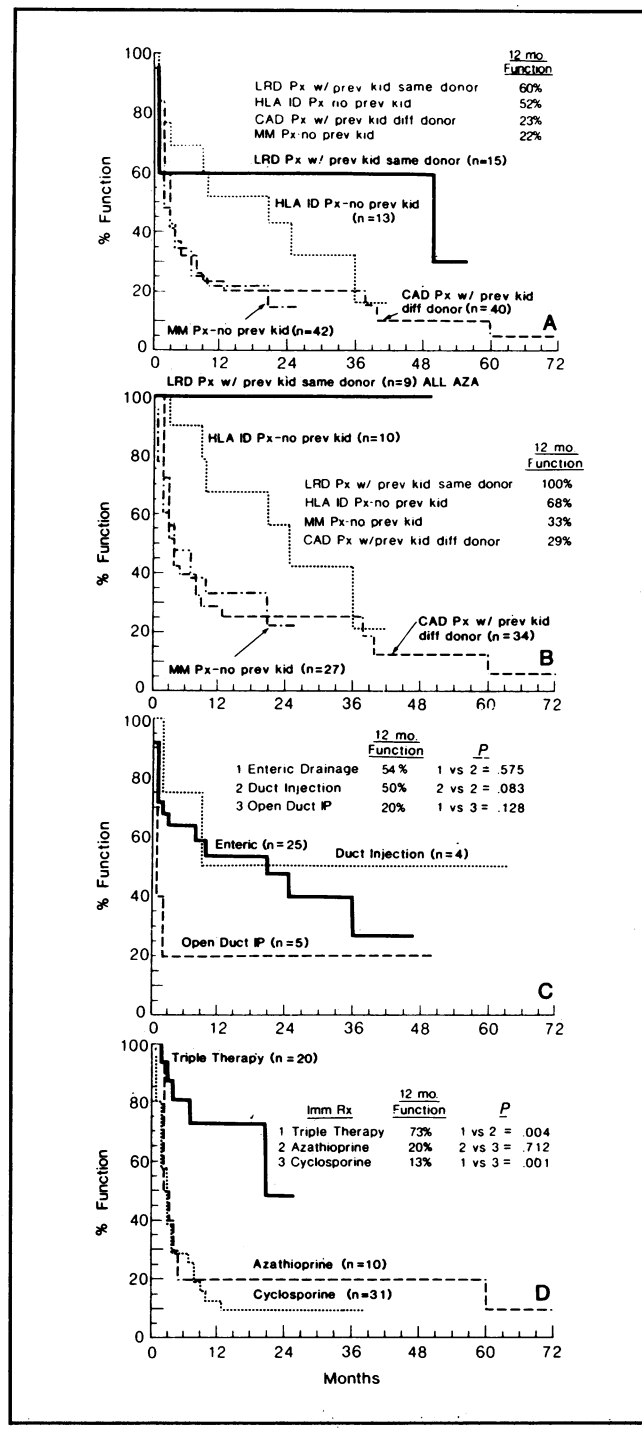

Figure 3.—A, Pancreas graft functional survival rates for all cases according to four categories: pancreas grafts (Px) from the same living related donor (LRD) as a previous kidney (prev kid); human leukocyte antigen-identical (HLA ID) sibling grafts into patients who had neither uremia nor a previous kidney transplant; mismatched (MM) related or cadaver (CAD) grafts in recipients of previous kidney transplants from a different donor or in those with no previous kidney transplants. **B,** Same as **A** except only technically successful grafts were analyzed. All AZA = all received azathioprine **C,** Functional survival rates according to technique of grafts from HLA-identical sibling or of mismatched related donors of a previous kidney. IP = intraperitoneal [drainage] **D,** Functional survival rates according to immunosuppressive therapy (Imm Rx) in nonuremic recipients of HLA-mismatched grafts from cadaver donors or mismatched related donors who have not previously given a kidney.

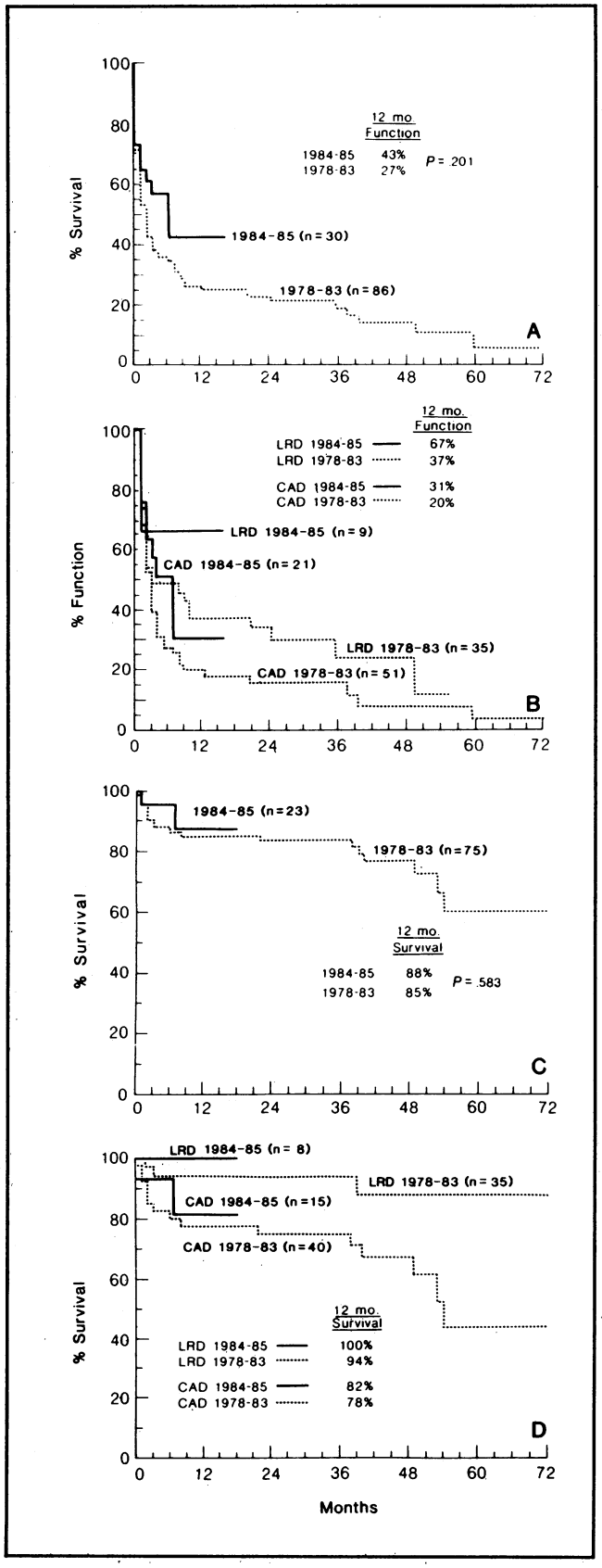

Figure 4.—Pancreas graft function survival rates (**A** and **B**) and recipient survival rates (**C** and **D**) according to year of transplant in all cases (**A** and **C**) and separately in recipients of transplants from either living related (LRD) or cadaver donors (CAD) (**B** and **D**).

normal or nearly normal glucose tolerance test results.[1,14] The mean plasma glucose values before transplantation and during the latest 24-hour profiles and orally administered glucose tolerance tests done in 15 currently insulin-independent recipients whose grafts were functioning at one year and more are shown in Figure 6 and compared with the results obtained in normal persons. The mean plasma glucose levels in pancreas transplant recipients are within the normal range but tend to be on the high side. Some recipients have absolute euglycemia, whereas others who have functioning grafts and are insulin-independent have values that are definitely above the normal range, as reflected in the standard deviations from the mean for the entire group.

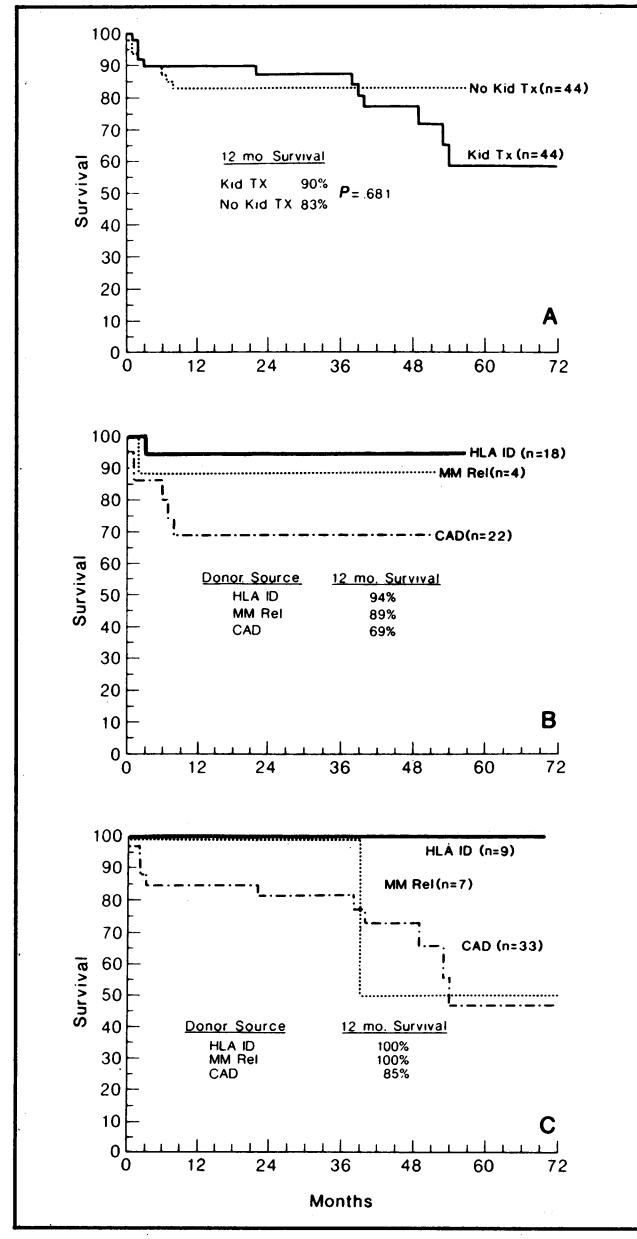

Figure 5.—Patient survival rates after pancreas transplantation, **A**, in those with (Kid TX) or without previous kidney grafts (No Kid TX), **B**, in those with previous kidney grafts according to pancreas donor source and **C**, in those without previous kidney grafts according to pancreas donor source. CAD = cadaver, HLA ID = human leukocyte antigen-identical, MM Rel = mismatched related

All patients have had detailed studies of eye, nerve and kidney function before and serially after pancreas transplantation.[15] Of the four patients whose pancreatic grafts functioned for more than four years, two had lesions noted by light microscopy that were typical of early diabetic nephropathy in kidney grafts transplanted nearly six years before the pancreas. In both patients, follow-up biopsy specimens appeared to show regression of the lesions. A possible influence of the pancreas transplant on diabetic retinopathy is difficult to ascertain in most patients, since either proliferative retinopathy was present—a stage where the eye disease is probably self-perpetuating independent of the degree of metabolic control—or the recipients had involutional retinopathy, which is also probably not influenced by metabolic control of diabetes. However, of three patients with preproliferative retinopathy who have been followed for more than a year, improvement occurred in two who were normotensive but not in one who had hypertension. Of four with proliferative retinopathy, three showed worsening (two had hypertension) and only one had improvement. Even though a beneficial effect of pancreas transplantation on retinopathy has not been shown, visual acuity improved in 8/16 patients (50%) with functioning grafts followed for more than a year and was stable in five patients (31%); only three had worsening (19%). In contrast, of 13 patients whose grafts failed early, 6 had worse vision at one year (46%) and none showed improvement. Neurologic studies at one year in patients whose grafts functioned did not show any significant changes in regard to quantitative measurements of autonomic function. An overall assessment, however, of neurologic status in 15 patients with functioning and 13 with failed grafts showed that 5 of the former were better (33%) while none of the latter were better, and only 1 with a functioning graft deteriorated (7%) compared with deterioration in 6 whose grafts failed early (46%).

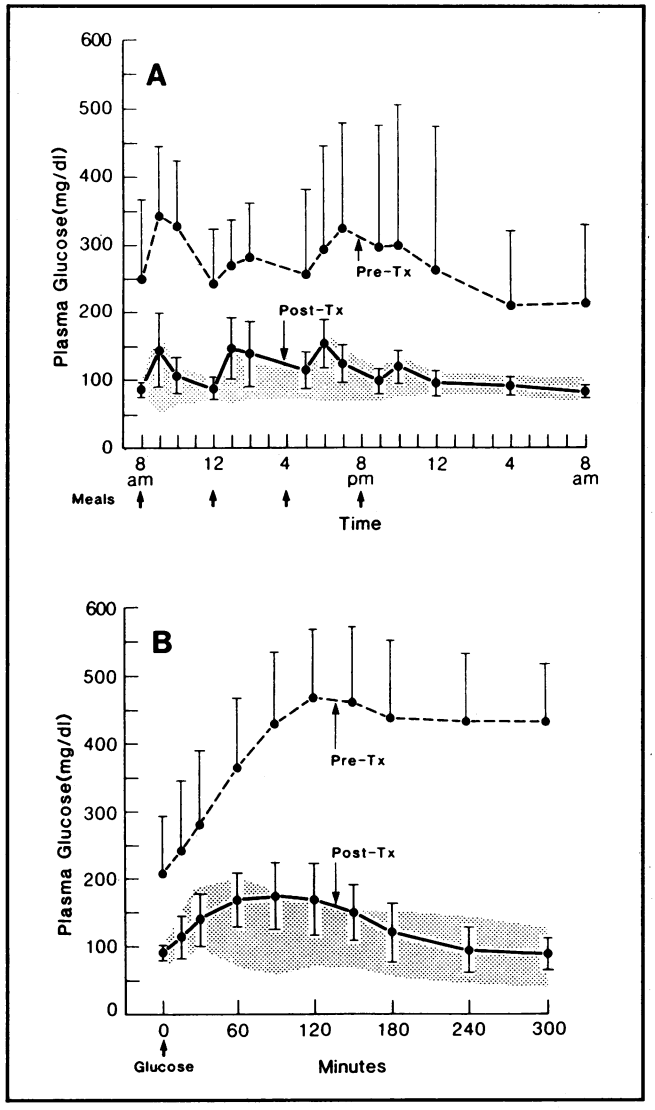

Figure 6.—Results (mean ± standard deviation [SD]) of metabolic studies in 18 patients with diabetes mellitus who have currently functioning pancreas grafts studied before (while on insulin therapy [Pre-Tx]) and at ≥1 year (12 to 80 months, mean 26 ± 21 months) after the transplant (no longer taking insulin; Post-Tx): **A**, 24-hour metabolic profile results and **B**, oral glucose tolerance test results. The shaded areas indicate the range (2 SD from mean) of values in 38 metabolic profiles and 42 oral glucose tolerance tests carried out in normal persons.

Discussion

Most pancreas transplants have been done in patients with diabetes who have far advanced complications, and most have had end-stage diabetic nephropathy treated with a kidney transplant either before or simultaneously with the pancreas transplant (see D. E. R. Sutherland and D. M. Kendall, "Pancreatic Islet Transplantation—Registry Report and Commentary," elsewhere in this issue). The benefit provided such patients by a pancreas transplant is uncertain, but because these patients already require immunosuppression to prevent rejection of the kidney, a pancreas transplant entails only the surgical risk and a case can be made for its application. A successful pancreas transplant may protect against the disease recurring in the transplanted kidney. However, it should be recognized that function deteriorates slowly and preexisting diabetic lesions in other systems are likely to take their toll before recurrent disease becomes a problem in the transplanted kidney.[16]

Although the present series began with application of a pancreas transplant to diabetic kidney-transplant recipients, we have changed our program so that most of the recipients now do not have uremia and have not had a kidney transplant. We attempt to identify persons who have diabetic complications that are not yet in the end stage but that, without intervention, will predictably be more serious than the possible side effects of a long-term immunosuppressive regimen. Most of our patients in recent years have been in this category (Figure 1). Although we initially thought that the use of cyclosporine would allow this group to be transplanted with a high success rate, we found that applying an immunosuppressive protocol (cyclosporine plus prednisone) that results in a high functional survival rate of renal allografts in recipients with uremia[17] did not prevent rejection of pancreas grafts. Twelve consecutive recipients of mismatched pancreas allografts who had had neither uremia nor a kidney transplant had graft rejection when immunosuppressed with a regimen of cyclosporine and prednisone alone. Persons who do not have uremia are more immunocompetent than those with uremia,[18] and we decided that the immunosuppressive regimens must be modified for transplantation in this group. For that reason, we began to use cyclosporine and azathioprine together because

experiments in animals had shown this combination to be very effective in preventing rejection of allografts.[19] The experience of other groups suggests that a cyclosporine and prednisone regimen is adequate for combined kidney and pancreas transplants in persons with uremia. However, in patients who do not have uremia, the use of cyclosporine and prednisone appears adequate only if the donor is an HLA-identical sibling, and even in this group rejections have occurred. For recipients of cadaver or mismatched related pancreas grafts (unless the relative was the donor of a previous kidney), the most effective protocol we have used has been a combination of cyclosporine, azathioprine and prednisone, with a 73% one-year actuarial functional survival rate for technically successful grafts. This protocol is particularly useful in patients with moderately advanced diabetic nephropathy because the cyclosporine dose can be adjusted downward to avoid superimposing cyclosporine nephrotoxicity on a diseased kidney and the azathioprine dose can be adjusted upwards to prevent rejection. This protocol has also been effective in preventing rejection of kidney transplants, with minimal toxicity to the recipients.[20]

In summary, our current approach is to transplant pancreas grafts to patients who do not have uremia whose diabetic complications are in the premorbid stage, to drain the graft of exocrine secretions into a hollow viscus and to give cyclosporine-azathioprine-prednisone therapy for immunosuppression. This protocol has evolved as the most successful we have tried.

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